A reassessment of diagnostic criteria and treatment of idiopathic urticarial vasculitis: a retrospective study of 47 patients

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doi:10.1111/j.1365-2230.2008.02891.x

Summary

Background. Urticarial vasculitis (UV) is an uncommon type of chronic urticaria (CU), which exhibits leucocytoclastic vasculitis. Painful and long-lasting (> 24 h) weals associated with purpura or bruising are considered indicative of UV. It is often responsive to oral corticosteroids and poorly to oral antihistamines. Hypocomplementaemia and systemic involvement are also commonly reported.

Aims. To diagnose patients with UV histologically and then compare their clinical features and response to various treatment regimens.

Methods. Biopsies were taken from 312 subjects with CU unresponsive to oral antihistamines; of these, 47 were histologically diagnosed as having UV. Biopsies were taken irrespective of the clinical features of weal eruption. Other diseases known to be associated with small-vessel vasculitis had previously been excluded.

Results. Individual weals lasted < 24 h in 57.4% of patients, and pain or tenderness was reported only by 8.6%. Extracutaneous features were present in 81%, hypocomplementaemia in 11% and abnormalities of other laboratory parameters (i.e. raised erythrocyte sedimentation rate, microscopic haematuria) in 76.6%. Hydroxyzine was effective in only one patient. Both oral corticosteroids and cinnarizine were effective in a high percentage of the patients.

Conclusion. This diagnostic approach allowed us to identify a large group (47 patients) with UV. Most did not present the clinical (prolonged duration of weals and bruising) and laboratory features that have previously been described as characteristic of UV. Cinnarizine was found to be a valuable treatment option.

Introduction

Urticarial vasculitis (UV) is believed to be an uncommon subset of chronic urticaria (CU) that is associated with leucocytoclastic vasculitis.[1–3] UV is most often idiopathic, although it has been described in association with connective tissue diseases (systemic lupus erythematosus and Sjögren's syndrome), neoplasia (monoclonal gammopathy and lymphoma), chronic infection with hepatitis virus A, B and C, Epstein–Barr virus and *Borrelia burgdorferi*, drugs (cimetidine, fluoxetine, procainamide, atenolol, sulfamethoxazole, paroxetine, sodium valproate, ciprofloxacin and zidovudine), and serum sickness-like diseases.[4]

Idiopathic UV can be further subdivided into normocomplementaemic UV (NUV) and hypocomplementaemic UV (HUV). NUV can be associated with systemic symptoms such as renal damage, arthralgia and other problems, but less often and with less severe damage than found with HUV.[4,5]

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Conflict of interest: none declared.

Accepted for publication 11 February 2008

Pathogenesis is presently believed to result from the formation of immune complexes that deposit in blood-vessel walls. The antigens eliciting the formation of these antibodies are as yet unknown. This process is followed by activation of different blood cell types leading to the features of leucocytoclastic vasculitis.[2,3]

Clinically, UV is characterized by long-lasting (> 24 h) and painful and/or tender weals associated with purpura or dusky discoloration of the skin.[6–8] It is often poorly responsive to oral antihistamines,[2] and prolonged administration of oral corticosteroids is often needed to provide relief; however, these have the drawback of long-term toxicity. Current knowledge of this disorder comes only from investigations that enrolled small groups of patients[1–3,6–8] with these characteristic clinical features. Only one study enrolled a large group of 72 patients.[4]

The aim of the present retrospective study was to diagnose UV histologically in skin biopsies taken from patients with CU resistant to oral antihistamines, irrespective of the presence of weal eruption. The clinical and laboratory characteristics of these patients were later assessed. The use of oral antihistamines, corticosteroids and cinnarizine as treatment options was evaluated.

Methods

All patients had been referred to the Allergy or Dermatology Unit of the Spedali Civili or the Nephrology and Immunology Unit of the San Carlo Hospital between 1996 and 2006, because of CU unresponsive to oral antihistamines. Responsiveness was assessed after at least 3 months of administration of the drug at full dosage. No patient was given corticosteroid, immunosuppressive or systemic treatments before undergoing biopsy. Biopsies were taken from patients even if they did not meet other widely accepted criteria for urticarial vasculitis: (i) individual lesions lasting > 24 h, associated with pain or tenderness; (ii) purpura or dusky discoloration of the skin; and (iii) resolution with hyperpigmentation.[9] All patients enrolled in the study had no clinical or serological evidence of other diseases known to be associated with small-vessel vasculitis. Duration and symptoms of any weal eruption and signs and/or symptoms suggesting systemic involvement were carefully registered on a standardized questionnaire.

All biopsies were taken from weals lasting < 24 h, and all histological samples were examined at the dermatology department of the Spedali Civili. A diagnosis of UV was made if neutrophilic or mixed infiltrate of lymphocytes, eosinophils, and neutrophils with either focal small-vessel neutrophilic vasculitis (identified by neutrophilic dominant infiltrate affecting small vessels accompanied by the changes of 'fibrinoid necrosis') or perivascular nuclear debris without fibrin deposits and with or without extravasated red blood cells were seen.[10] In addition, oedema of collagen bundles in the upper dermis and injury and swelling of endothelial cells with disruption of the vessel wall were observed in a few histological samples.[10]

All patients affected by idiopathic UV underwent the following laboratory examinations. Routine blood chemistry haematology, urinalysis, erythrocyte sedimentation rate (ESR), C-reactive protein, rheumatoid factors (Ra test, Waaler Rose test), cryoglobulins and CH50 were performed by standard methods. C3 and C4 were measured by nephelometry (Array Protein System; Beckham, Brea, CA, USA). Antinuclear antibodies (ANA) were investigated by indirect immunofluorescence on Hep-2 cells (Kallestad-Carlo Erba, Milan, Italy). Counterimmunoelectrophoresis using a rabbit thymus extract (Peel-Freez, Rogers, AK, USA) was used to test for antibodies against extractable nuclear antigen, except for Ro/SS-A autoantibodies, which were tested by Ouchterlony immunodiffusion. Anticardiolipin (aCL) and anti-β2 glycoprotein I antibodies were tested by ELISA. Total serum IgE was measured by the paper radioimmunosorbent test (PRIST Kit; Pharmacia Diagnostics AB, Uppsala, Sweden) and in selected cases, specific serum IgE levels were measured by radioallergosorbent test (CAP System; Pharmacia). Antineutrophil cytoplasmic antibodies were determined by indirect immunofluorescence and by ELISAs specific for antiproteinase 3 and antimyeloperoxidase antibodies (Euroimmun, Lübeck, Germany).

If there was clinical or laboratory findings indicated that there was systemic involvement, the following tests were also carried out: spirometry, echocardiography, urea breath test for *Helicobacter pylori*, oesophagogastroduodenoscopy, renal ultrasonography, conventional radiography of the skeleton, and chest X-ray.

All patients received oral H1 antihistamines (hydroxyzine 25 mg/day) as first-line treatment. If a patient had been previously treated by with hydroxyzine before entering the study, and had shown only partial or no response, desloratadine 5 mg/day was given. If complete and persistent remission was not achieved within 6 months, patients were treated with cinnarizine 25 mg three times daily or corticosteroids (prednisolone 0.2–0.5 mg/kg/day) together with oral antihistamines (hydroxyzine or desloratadine). The dosage of cinnarizine was chosen on the basis of beneficial effects

previously reported in the treatment of cold urticaria.[11] These treatments were continued until complete and sustained remission was achieved, and then patients entered into a follow-up period. In cases of partial or no remission after a treatment period of up to 6 months, patients were treated with various combinations of antihistamines, cinnarizine, corticosteroids, montelukast, ciclosporin A and azathioprine.

Results

Over the 10-year study period (1996–2006), biopsies were taken from 312 patients with CU unresponsive to oral antihistamines; of these, 47 patients (15.1%) were found to have histological results consistent with the diagnostic criteria of UV (Fig. 1). These patients (33 female, 14 male; median age at time of diagnosis of 45 years, range 12–79) all had CU lasting > 6 months with daily eruption of weals (Fig. 2). The clinical features had been present for a median time of 4 years (range 15 days–13 years) before diagnosis. Hypocomplementaemia was found in five patients (11%): low C3 and CH50 levels in two and low C3, C4 and CH50 in three.

The clinical features and laboratory findings of the patients and their incidence in the two subgroups (NUV and HUV) are described in detail in Table 1.

Weals lasted > 24 h in 20 (42.6%) patients. Itching was the only symptom in 38 (80.6%) patients, whereas six (12.8%) patients had itching and burning and four (8.6%) patients experienced pain or tenderness (Table 1). In seven patients (14.9%), the urticarial features appeared not only spontaneously, but could also be triggered by physical exercise (two) and dermographic stimulus (five). Weal eruptions were accompanied by angioedema in 21 (44.7%) cases (Table 1).

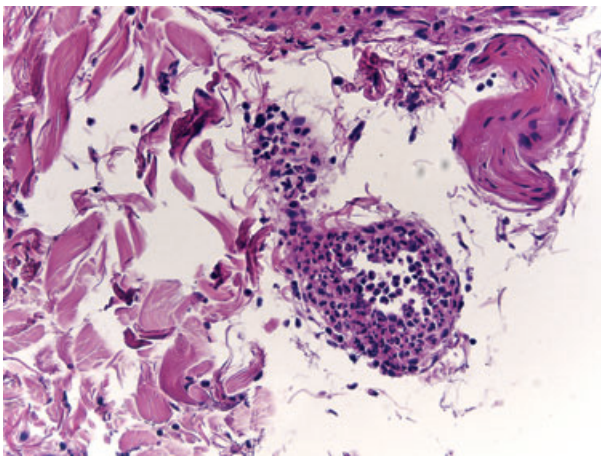

Figure 1 Leucocytoclastic vasculitis showing invasion of neutrophilic infiltrate into vessel wall with vessel injury and perivascular nuclear dust (haematoxylin and eosin, original magnification × 20).

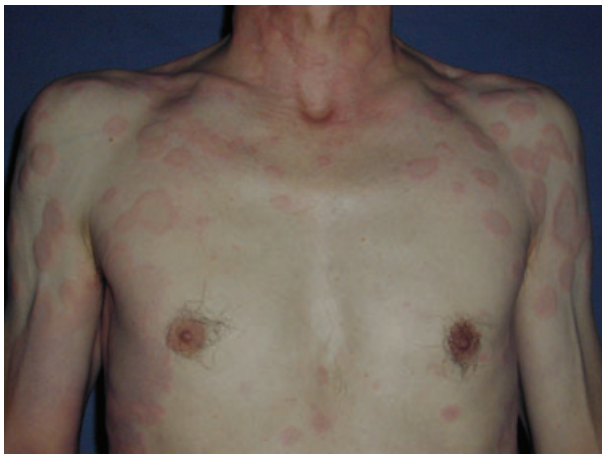

Figure 2 Spreading weals on the trunk.

One or more extracutaneous features were found in 38 patients (81%), with arthralgia and fever being the most common (Table 1).

Laboratory findings were abnormal in 36 (76.6%) patients: ESR elevation in 20 (42.6%) was the most common finding (Table 1). In nine patients (19.1%), microscopic haematuria was found, but no patient developed renal failure.

None of the patients with altered immunological tests (ANA, aCL) developed full-blown autoimmune disease. Other laboratory and instrumental investigations were always negative or within normal ranges.

Oral hydroxyzine and oral desloratadine were given to 31 and 16 patients, respectively. Only one patient with NUV, who had been previously resistant to desloratadine, achieved complete and persistent clinical remission after 6 months' therapy with hydroxyzine. The remaining patients had only partial and temporary remission. Of these, 39 to be treated with cinnarizine or with a combination of oral corticosteroids and H1 antihistamines for 4–6 months. Of the 19 patients treated with cinnarizine, 13 achieved complete remission. The clearance rate was similar to that found in the group treated with oral corticosteroids plus H1 antihistamines (13 out of 20). Remission, if any, was always persistent at follow-up (median 4 years; range 6 months–10 years) without recurrence. All patients treated with anti-H1 antihistamines or cinnarizine experienced various degrees of drowsiness but interruption of therapy was never necessary. Other treatment-related adverse effects never occurred.

Table 1 Clinical and laboratory features of 47 patients with urticarial vasculitis.

	All patients (n = 47), n (%)	Patients with HUV (n = 5), n (%)	Patients with NUV (n = 42), n (%)
Duration of weals > 24 h	20 (42.6)	1 (20)	19 (45)
Angio-oedema	21 (44.7)	3 (60)	18 (43)
Papular lesions	10 (21.3)	1 (25)	9 (21)
Purpura, bruising or dusky discoloration	3 (6.4)	3 (60)	0 (0)
Pruritus	38 (80.6)	4 (80)	34 (81)
Pruritus and burning	6 (12.8)	1 (20)	5 (12)
Pain and/or tenderness	4 (8.6)	0 (0)	4 (8)
Arthralgia	18 (38.3)	4 (80)	14 (33)
Fever	17 (36.2)	3 (60)	14 (33)
Asthenia	11 (23.4)	4 (80)	7 (17)
Abdominal pain	2 (4.3)	1 (20)	1 (2)
Dyspnoea and/or cough	6 (12.8)	0 (0)	6 (14)
Rise in erythrocyte sedimentation rate	20 (42.6)	2 (40)	18 (43)
Microscopic haematuria	9 (19.1.)	1 (20)	10 (23.8)
Antineutrophil antibodies (≥ 1 : 80)	6 (12.8)	1 (20)	5 (12)
Anticardiolipin/anti-β2 glycoprotein I	1 (2.1)	1 (20)	0 (0)

HUV, hypocomplementemic urticaria vasculitis; NUV, normocomplementemic urticaria vasculitis.

Patients resistant to cinnarizine or corticosteroid plus antihistamines were treated with various combinations of antihistamines, cinnarizine, corticosteroids, montelukast, ciclosporin A and azathioprine. Results were variable and generally disappointing, and owing to the low number of patients assigned to each of these treatment regimens, they are not reported in detail.

Discussion

In this study, biopsies were taken from 312 patients with CU unresponsive to oral antihistamines, irrespective of the presence or duration of weal eruption and symptoms. This extensive approach allowed us to recruit 47 patients showing a high prevalence (15.1%) of unresponsive CU in the tested group, and few relevant differences from findings of previous reports in which biopsies had been taken using more selective criteria such as presence of long-duration (> 24 h) and characteristic symptoms (pain or tenderness) of the weal eruption and its association with purpura or dusky discoloration of the skin.[1–3]

In our study, female preponderance and mean age of patients were in general agreement with previous findings but, unlike these,[1,2,4,6,8] we found that weals lasted > 24 h in less than half of the patients. Pain or tenderness was reported by only a small minority of patients (8.6%), and burning (although always associated with itching) was also uncommon (12.8%). Purpura or dusky lesions were also seen in only a few cases. Angio-oedema was quite common (44.7%) and this occurrence was similar to that found in CU.[12]

Therefore, we believe that the duration and symptoms of individual weals should not be considered pivotal criteria[9] for the existence of UV, and that instead, a skin biopsy should be taken from all patients with CU unresponsive to antihistamines. Otherwise, if biopsies are restricted to cases with painful or burning weals with prolonged duration and purpura or bruising after resolution, a high proportion of patients could be missed, which has important implications for their investigation and management, particularly with respect to potential underlying or associated diseases.

In agreement with the literature,[2,4,13] ≥ 1 extracutaneous features were present in 81% of the cases, with arthralgia (38.3%) and fever (36.2%) being the most common. Unlike a few previous reports,[2,4] no involvement of the eyes was observed in the patients we studied.

Raised ESR was seen in a 42.6% of patients, a rate that is in agreement with the data of Mehregan *et al.*[4] but not with others,[8,14] who have reported higher percentages.

In Table 1, we describe in detail the clinical and laboratory characteristics of the patients with HUV and NUV involved in our study. Statistical analyses of these data were not feasible due to the low number (five) of patients with HUV. However, we emphasize that

duration and symptoms of the individual weals, incidence of angio-oedema, and serum and urinary abnormalities were quite similar in the two groups. However, in patients with HUV, there was a much more frequent association of weal eruption with purpura and dusky discoloration and with features of systemic involvement.

Desloratadine and hydroxyzine proved largely ineffective for the treatment of UV. A single patient who was resistant to desloratadine responded to hydroxyzine. This finding indicates that hydroxyzine may be effective in patients with sporadic UV resistant to other antihistamines, but spontaneous remission must also be considered. In our patients, the combination of desloratadine or hydroxyzine with oral corticosteroids was highly effective and the remission rate was higher than those reported in previous studies.[8,14] However, long-term use of corticosteroids has a significant risk of toxicity. We therefore also investigated the efficacy and tolerability of cinnarizine, which has a low toxicity even after prolonged treatment, and has previously been found to be effective in the treatment of CU and cold urticaria.[11,15] This drug has both antihistaminic and vasoactive properties, and is also an inhibitor of complement activation. We found that high numbers of patients appeared to respond to cinnarizine, at a similar rate to those responding to the combination of oral antihistamines and corticosteroids. Therefore, this piperazine-derived drug seems to represent a valuable treatment option for UV, although a well-designed comparative study with corticosteroids will be needed to confirm this.

Conclusion

It seems likely that idiopathic UV is more common than previously thought, and further investigations using skin biopsy as a selective criterion for patients enrolled in studies of UV are needed. The need for reassessment of this clinical entity was also emphasized recently by Loh *et al.*,[9] who showed that biopsy specimens of lesions with characteristic clinical features of UV more commonly have a predominantly lymphocytic infiltrate with eosinophils than of leucocytoclastic vasculitis.[9] Reassessment of the clinical and laboratory features of this disease would lead to a better knowledge of its pathogenesis. It is important to note that both cinnarizine and the combination of oral corticosteroids and H1 antihistamines were effective; however cinnarizine is preferable because of its lower toxicity.

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